EXHIBIT B

Histopathology of Rosacea

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Biopsies from 108 patients with rosacea have been examined and the histological changes correlated with the clinical condition. There is no single histological feature unique to rosacea but it is characterized by a combination of several histological signs; various types of rosacea represent an exaggeration of one or another aspect of the basic pathological changes; the disease is neither primarily a folliculitis nor an inflammatory disorder of small blood vessels. There is disorganization of the upper dermal connective tissue with edema, disruption of fibers, and frequently severe elastosis. A comparison of 39 rosacea patients with 39 controls for solar elastotic change indicated an increased incidence and degree of elastosis in rosacea patients. It is suggested that loss of integrity of upper dermal connective tissue may permit vascular dilatation and that this may have an important role in the pathogenesis of the disease.

THERE is little knowledge as to the etiology and pathogenesis of rosacea. Factors considered have included the seborrheic state, gastrointestinal disturbances, and psychological disorders (Beerman and Stokes,[1] and Hellier[2]) and the mite *Demodex folliculorum* (Ayres and Ayres[3]; Russell[4]; and Spickett[5]). The persistent erythema, the telangiectasia, and the facial flushing suggest that the small blood vessels of the face are involved either primarily or secondarily; Sabye[6] suggested that prolonged climatic exposure caused vascular injury.

A previous investigation indicated that edema and disorganization of the upper dermis were conspicuous histological features and that the degree of solar elastosis was excessive (Marks[7]). In this study we have examined biopsies from 108 patients with rosacea to further define the role of the above factors.

Patients

Biopsies were taken from 108 patients, special care being taken to record the type of lesion (Table 1). For the purpose of this study rosacea was defined as follows: A disease of the skin mostly affecting the cheeks and often the chin, nose, and forehead characterized by persistent erythema and often telangiectasia with acute episodes of edema, papules, and pustules in some cases. Patients with comedones, scars, or cysts were diagnosed as having acne even though there was a background of erythema, and excluded. Similarly patients with perioral dermatitis were not included. For evaluation of the degree of elastotic change, portions of skin were obtained from biopsies and excisions from patients with a variety of skin complaints undergoing routine minor surgical procedures matched for age, sex, and site of biopsy (Table 2). The following were the diagnoses in this control group: compound nevus, ten; seborrheic wart, six;

Table 1.—*Types of Rosacea in This Study*

	Papular	Erythemato-telangiectatic	Rosacea of Nose
Men	44	12	7
Av age, yr	50.5	47.5	55.3
Women	30	12	3
Av age, yr	46	432	47.6
Total No. of Patients	74	24	10

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Table 2.—*Age and Sex, and Site of Biopsy of Matched Rosacea and Control Patients*

Patients	Av Age	Men	Woman	Chin	Cheek	Forehead	Nose	Neck
Rosacea	48.4	13	26	4	18	11	5	1
Controls	49.3	11	28	4	15	13	6	1

Table 3.—*Results of Questionnaire**

Scoring System	Score
Occupation†	
Mostly (sometimes) outside more than 2 yr	2(1)
Mostly (sometimes) outside more than 5 yr	5(2)
Mostly (sometimes) outside more than 10 yr	10(4)
Mostly (sometimes) outside more than 20 yr	20(8)
Living in a sunny country	
2 - 5 yr	10
5 - 10 yr	20
More than 10 yr	30
Outdoor activities	
Keen on outdoor activities (in past)	5(3)
Keen sunbather	6
Tans easily	—5
Burns easily	2

The mean score for the rosacea patients was 7.91 and the mean score for the controls was 12.07.

Complexion, Hair and Eye Color in Rosacea and Control Patients

Complexion	Rosacea	Controls
Light	12	15
Medium	23	14
Dark	0	1
Hair		
Light	8	11
Medium	19	13
Dark	8	5
Eyes		
Light	23	18
Medium	2	0
Dark	10	12

* Thirty-five rosacea patients and 30 controls replied to the questionnaire.

† *Exposure:* With regard to exposure the questions concerned occupation, periods spent in a sunny country, and other outdoor activities and preferences. A scoring system was used to evaluate the degree of exposure.

Table 4.—*Results of Comparison of Matched Rosacea and Control Sections for Elastosis*

No. of Specimens	Score 0	+1	−1	+2	−2	Total Points
9	X					0
9		X				+9
2			X			−2
12				X		+24
7					X	−14
Total for all matched specimens						+17

basal cell epithelioma, ten; keratoacanthoma, three; pyogenic granuloma, one; cyst, one; lentigo, one; sebaceous gland hypertrophy, one; benign warty hyperplasia, one; hemangioma, one; nevus sebaceous, one; and lupus erythematosus, one. Thirty-nine such matched specimens were obtained. Information concerning occupation, exposure to the sun, residence in sunny countries, and skin coloring was obtained by a questionnaire completed by the patients (Table 3). There was a higher estimated exposure in the control group but the coloring of the two groups was approximately similar.

Methods

Biopsies were taken after local infiltration with 1% lidocaine. An ellipse of skin, approximately 1 × 0.5 cc, was surgically removed and fixed in 10% formol saline. Seventy five specimens were sectioned routinely. Serial sections were cut from 24 specimens of papular or papulopustular lesions, eight of these at 20μ intervals being mounted. A further seven specimens were sectioned obliquely to show the epidermis, upper dermis, and hair follicles, another two were cut horizontally at various levels to show numerous follicles in cross section.

All sections were stained with hematoxylin and eosin. Sections from 11 unmatched rosacea patients and all the sections from the 39 matched rosacea and 39 control patients were stained with the Verhoeff's technique for elastic tissue.

Evaluation of the Amount of Solar Elastosis

Solar elastosis was identified in the hematoxylin and eosin stained sections as altered dermal connective tissue in the papillary and upper dermis; this appeared either fragmented and disorganized or gave a homogenized appearance and tended to be more basophilic than the surrounding dermis. The degree of elastotic degeneration in sections from rosacea patients and controls was compared by directly contrasting paired sections from each group matched for age, sex, and site of biopsy. The following scoring system was devised.

0, No difference in the degree and extent of elastosis in the two section.

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+1, Slightly more elastosis in the rosacea section.

−1, Slightly more elastosis in the control section.

+2, More than twice as much elastosis in the rosacea than the control section.

−2, More than twice as much elastosis in the control than in the rosacea section.

The findings of this comparison technique are given in Table 4.

Observations

Papular Rosacea.—Biopsies of papules or papulopustules from 74 patients were obtained.

Inflammatory Cell Infiltrate.—A conspicuous feature was the presence of a variable amount of inflammatory cell infiltrate in the upper and middermis consisting mainly of lymphocytes and histiocytes in varying proportions. Some sections also included considerable numbers of polymorphonuclear leukocytes, plasma cells, and giant cells. Giant cells of a foreign-body type which were vacuolated but contained no recognizable foreign material were seen in 11 (14%) sections; in one section they were seen in great numbers (Fig 1). The infiltrate was usually a loosely arranged collection of cells without a particular pattern (Fig 2); however, in eight sections (11%) it was of tuberculoid type. In general, in the larger and older papules there was more cellular infiltrate with a more organized type of arrangement. In six biopsies taken from newly formed small papules the only conspicuous feature was a small amount of perivascular lymphocytic infiltrate.

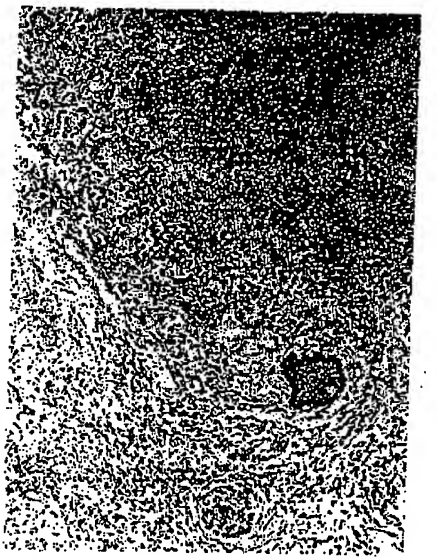
Pilosebaceous Apparatus: Demodex Folliculorum.—Among the 74 biopsies, 15 (20%) showed an abnormality of the hair follicle. In ten there was partial disruption of the follicular epithelium and polymorphonuclear leukocyte invasion of the substance of the pilosebaceous unit. This disruption was usually high in the follicle and was the histological counterpart of the pustular lesions noted clinically (Fig 3). In five, however, there was total destruction of the follicle with an intense granulomatous inflammatory reaction but there was no evidence as to the agent responsible for this event.

Of the 24 specimens serially sectioned six (25%) showed areas of acute folliculitis, while in the remainder the inflammation was entirely independent of the pilosebaceous apparatus. In the seven biopsies cut obliquely and in the two cut horizontally there was no primary abnormality of the numerous pilosebaceous units seen.

With 37 specimens (51%) the infiltrate was partially distributed around the hair follicles, and often the perifollicular localization appeared incidental to the cells collecting perivascularly in the right perifollicular plexuses (Fig 4).

Fourteen biopsies (19%) contained recognizable parts of the mite demodex folliculorum in the lumina of the follicles. No other abnormal feature was seen in these sections and it was particularly noticed that only one of the infested follicles showed a folliculitis; there was no evidence that the demodex had penetrated the follicular epithelium. Fifty-eight biopsies (78%) showed follicular plugging with a loose meshwork of keratin.

Fig 1.—Papular rosacea with heavy chronic inflammatory infiltrate including numerous giant cells (hematoxylin and eosin, × 100).



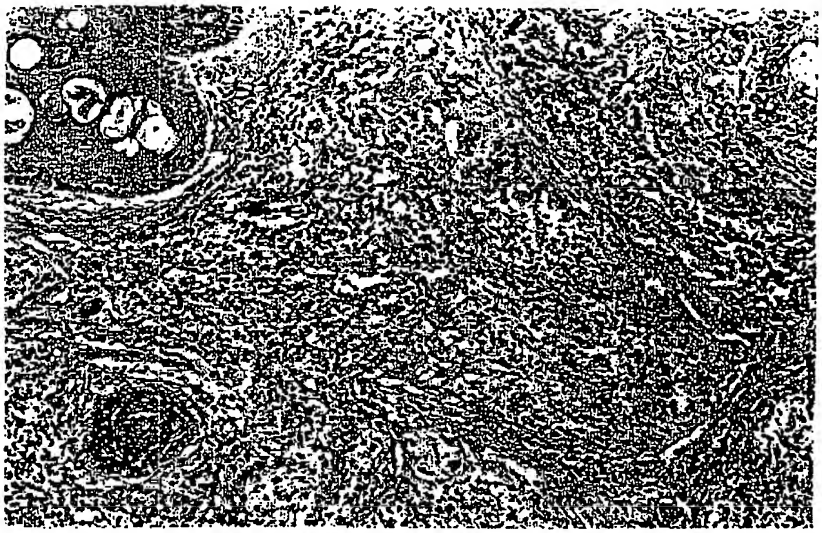
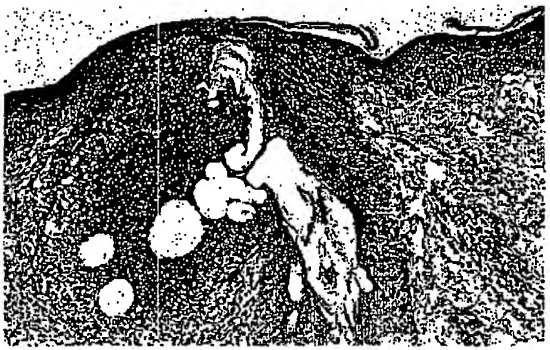


Fig 2.—Papular rosacea showing a diffuse lymphohistiocytic infiltrate. Note nearby uninvolved hair follicle. (hematoxylin and eosin, × 200).

Fig 3.—Papulopustular rosacea with an abscess containing many polymorphonuclear leukocytes high in the wall of the follicle. There is also a Demodex deeper down in the follicle, away from the inflammation (hematoxylin and eosin, × 100).



The Vessels.—Sixty-three sections (85%) included a pronounced vascular dilatation; this was very marked in 14 (21%). The greatest dilatation of the vessels occurred in the upper and papillary dermis, some vessels being of enormous size. Some of the vascular channels were lymphatics but in general these were more obvious in the middermis rather than in the upper dermis and papillae. The dilated vessels were often found amid edematous, disrupted, and elastotic connective tissue (see below). Only one specimen showed evidence of blood vessel damage with several vessels showing eosinophilic smudging of outline and endothelial cell swelling.

The inflammatory infiltrate was predominantly perivascular in 19 (26%) (Fig 5) and was partially perivascular in a further 42 sections (57%) loosely set in edematous tissue.

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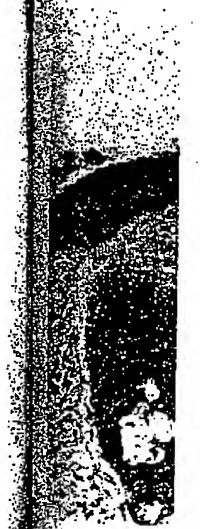

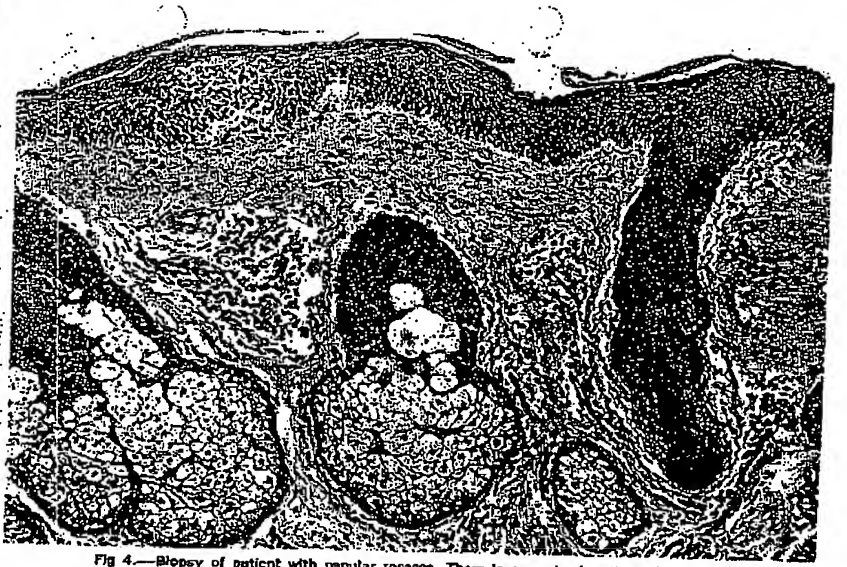

Fig 4.—Biopsy of patient with papular rosacea. There is a predominantly perivascular inflammatory infiltrate which also surrounds one follicle (hematoxylin and eosin, × 25).

Fig 5.—Early papular rosacea with a moderate perivascular chronic inflammatory cell infiltrate (hematoxylin and eosin, × 400).

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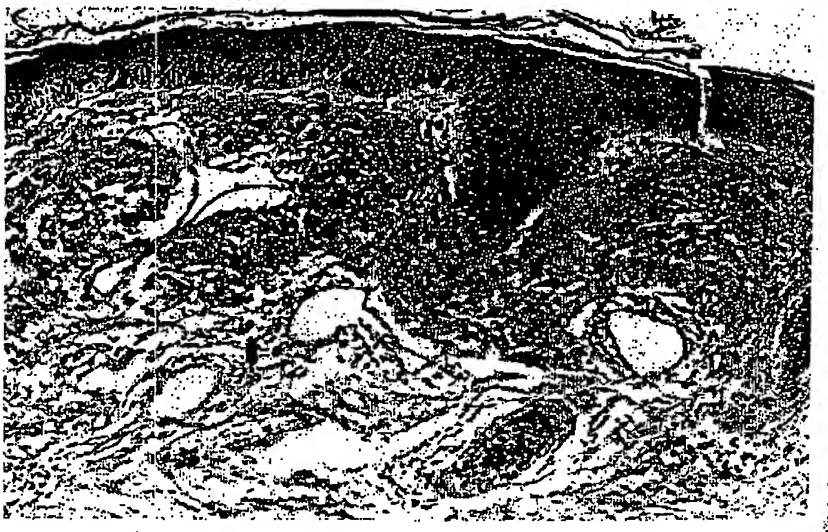
Erythematotelangiectatic Rosacea.—Biopsies from 24 patients with persistent erythema and telangiectasia and a variable amount of swelling were examined. The histological changes in general resembled those of the papular type of rosacea. However, the cellular infiltrate was mainly perivascular and the predominant cell type was the lymphocyte.

The most striking feature was a vascular dilatation which was very pronounced in nine (38%) (Fig 6). In those patients with very obvious telangiectasia, clinically there was a corresponding dilatation of vessels in their biopsy sections. Most of these dilated channels were in the upper dermis which also showed disruption of connective tissue architecture. The upper dermis was reduced in bulk, edematous, and frag-

Fig 6.—Erythematotelangiectatic rosacea showing grossly dilated and irregular vascular channels in the upper dermis. There is also solar elastosis and some disruption of the normal connective tissue (hematoxylin and eosin). × 100).

Fig 7.—Erythematotelangiectatic rosacea showing prominent solar elastosis and telangiectasia (hematoxylin and eosin, × 200).



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mented with attenuated strands of collagen loosely strung between the vessels. Solar elastosis was a prominent accompanying feature (Fig 7) (see below).

Results of Comparison for Degree of Elastosis.—From Table 4 it may be seen that more elastotic change was found in the rosacea patients rather than in the controls. The controls had more sun exposure than the rosacea group and this gives added significance to these results. Another assessment (uncontrolled) of elastosis was performed on a total of 104 biopsies; 33 showed a severe degree of elastotic degeneration while only nine failed to show any evidence of this change.

Other Clinicopathological Correlations

Swollen, reddened noses from ten patients were biopsied. None of these had a severe degree of rhinophyma but were chosen as early examples of this process. All ten showed a pronounced telangiectasia and in nine there was elastotic degeneration that was severe in three. There was also a heavy inflammatory cell infiltrate which was diffusely scattered through the middermis and upper dermis. In two sections there were a few small clusters of polymorphonuclear leukocytes with invasion of nearby hair follicles. Four of these sections showed a mild- to moderate degree of sebaceous gland hypertrophy.

Facial edema was a feature of several of the patients in this series but it was especially noted in five. Sections from these patients showed no distinguishing features although edema and telangiectasia were conspicuous. In one there was reduplication of the small blood vessel endothelium while in another there appeared to be a granulomatous cellular infiltrate in the lumina of some of the vascular channels (possibly lymphatic) in the deeper part of the dermis.

The chin of one patient was diffusely thickened and was reminiscent of the nasal thickening seen in rhinophyma. In the biopsy there was conspicuous sebaceous gland hyperplasia, telangiectasia, and solar elastosis, there was also a scattered infiltrate of lymphocytes and histiocytes. A patient with mild erythematotelangiectatic rosacea also had swollen reddened earlobes for many years; a biopsy from one of these showed pronounced edema and telangiectasia throughout the dermis and a small amount of inflammatory cell infiltrate.

Two sections were available from patients who had used potent corticosteroid preparations topically, they presented with a very striking persistent facial redness and telangiectasia as described by Sneddon (1969).[8] Telangiectasia and loss of normal architecture in the upper dermis were prominent features of these sections.

Comment

There are few reports of the histological changes in rosacea and little attempt has been made to correlate such changes with clinical findings. The available literature deals mainly with the granulomatous nature of the inflammatory infiltrate and its occasional tuberculoid arrangement (Laymon and Schoch[9]; Laymon[10]; Michelson[11]; and Van Ketel[12]). Miescher[13] found that 64% of a series of 58 cases of papular rosacea included tuberculoid-type infiltrates, and he divided rosacea into erythematous, telangiectatic, a glandular hyperplastic type leading to rhinophyma and a micronodular form associated with acneiform papules.

Histological Diagnosis of Rosacea

The most common features seen in biopsy material from all clinical types of rosacea are: a variable amount of lymphohistiocytic inflammatory infiltrate arranged loosely around the upper dermal blood vessels, telangiectasia, edema, elastosis, and disruption of the architecture of the upper dermis. These features in combination should suggest a histological diagnosis of rosacea. More extensive and dense inflammatory cell infiltrates with numerous histiocytes and occasional giant cells may indicate papular rosacea, while a pronounced upper dermal dystrophy and telangiectasia suggests the erythematotelangiectatic variety.

Pathogenetic Considerations

Role of the Hair Follicle.—Only 20% of the material from our patients with papular rosacea showed disruption of hair follicles. Our findings strongly suggest therefore, that

there is no basic follicular abnormality in rosacea. Two thirds of this 20% had a small abscess in the upper part of the follicle corresponding to the clinical feature of pustulation. The remaining one third showed a more profound destruction of follicular structure with a resultant granulomatous inflammatory reaction; this may represent a healing stage of pustular folliculitis. Pustulation is considered to be a secondary phenomenon because of the small number of cases in which it was seen and because it was only detected in sections from patients with papular rosacea where there appeared to be other more profound and commonly seen changes. In many sections the perivascular inflammatory infiltrate in the perifollicular plexuses created a false appearance of folliculitis.

Role of Demodex.—The mite *D folliculorum* is thought to occur more frequently in rosacea patients than in normal population (Russell[4] and Spickett[5]). However, the mite is commonly found in other facial dermatoses. The finding of *Demodex* in only 19% of our biopsy material and its absence from areas of inflammation in sections in which it was found are much against a significant role for this organism in this disease. A granulomatous tissue reaction to *D folliculorum* is known to occur in the marsupial mouse (Nutting and Beerman[14]) and in other animals (Nutting[15]). However, there was no suggestion that the human variety of *D folliculorum* was responsible for such a reaction in our material. It is possible that a local delayed hypersensitivity response to *Demodex* antigens diffusing through the intact follicular epithelium is partly responsible for the inflammatory component of the disease but one would expect that all follicles containing the mite would show inflammation and this is not seen. However, until suitable antigens are available this hypothesis cannot be tested.

Role of the Small Vessels.—In this study there is no evidence that primary vascular damage occurs in rosacea. The peripheral lesions of disseminated rosacea may include damage to small blood vessels with endothelial cell swelling and even fibrinoid degeneration (Marks and Wilson-Jones[16]). No comparable lesions were seen in the facial lesions of this series. Apart from the above considerations there is the functional adequacy of the vessels to be considered. This process of upper dermal disorganization could account for the erythema and telangiectasia which are cardinal clinical features of rosacea. It is a common clinical observation that the cheeks are cool in a rosaceous subject and this has been confirmed by direct thermometry (Borrie[17]). Although there are no published quantitative observations it seems probable that the congestion of the dermal blood vessels is associated with a slow ambient flow of blood. The sluggish circulation is probably due to pooling in the enormously dilated vascular channels of the subpapillary venous plexus. The vascular dilatation is not due to intrinsic disease of the vessels but appears to be due to lack of a surrounding firm connective tissue framework allowing passive dilatation.

Clinical aspects of rosacea such as swelling of the affected areas and even pronounced lymphoedema are reflected in histological sections as edema and lymphatic dilatation. The dilated lymphatics may be the result of the same dermal dystrophy as causes the telangiectasia; the edema could result from their loss of efficiency as conduits.

Role of Solar Elastosis and Climatic Factors.—Solar elastosis appeared to be more frequent and of greater severity in rosacea patients than in controls. This confirms the impression gained previously (Marks[7]) that the histological change of elastotic degeneration was more obvious in patients with rosacea. No explanation for this observation is forthcoming from our observations. It is suggested that the elastosis contributes to the disorganization seen in the upper dermis.

Patients with rosacea often complain of burning and soreness when in the sun; 28% complained that the sun made them worse although increased sensitivity to ultraviolet light was not found (Marks[7]). In addition, the disease appears to be more common in subjects with fair complexions. Haxthausen[18] believed that climatic exposure was important in its etiology. Søbye[6] and Brodthagen[19] were also impressed with the role of exposure to the sun in the development of rosacea. It is possible that patients with this disease are more susceptible than normal to climatic stimuli and that the upper dermal changes are a result of their continued action.

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Rosacea of the Nose

The early examples of rosacea affecting the nose demonstrate changes similar to other types of rosacea; sebaceous gland hypertrophy is not a prominent feature. Acker and Helwig[20] in a review of the histology of 47 cases of rhinophyma found five with a basal cell epithelioma. Forty-one of the 47 showed sebaceous gland hypertrophy and one third showed telangiectasia. Rhinophyma with its enormous proliferation of sebaceous glands may represent the late changes of rosacea affecting the nose. One of our sections was derived from a man with an irregularly swollen, dark red chin that was reminescent of rhinophyma. Interestingly it showed a moderate degree of sebaceous gland hypertrophy as well as a considerable amount of inflammatory cellular infiltrate, telangiectasia, and elastosis. A similar but more severely affected patient—a woman, was described by Sams.[21]

It is possible to draw several important conclusions from our findings in this study: (1) There is no single histological feature unique to rosacea, but a combination of several findings makes this a likely diagnosis. (2) The different clinical types represent an exaggeration of one or another aspect of the basic histology. (3) There is no evidence from the histological material examined that the disease is either primarily a disorder of the pilosebaceous apparatus, or an inflammatory disorder of small blood vessels. (4) A prominent component of the histopathology of rosacea, observed in this study, was disorganization in the upper dermis.

Drs. S. C. Gold and K. V. Sanderson of St. George's Hospital allowed us to study their patients. The physicians of St. John's Hospital referred patients to us for study. Mr. P. Hammond, Mr. R. Truman, and Mr. P. Manning of the Department of Morbid Anatomy, St. George's Hospital, gave technical assistance.

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